REMARKS/ARGUMENTS

Pending Claims

Claims 1-17, 31-32, 40-41, and 49-64 are pending. Claims 1-15 and 49-58 are allowed.

Discussion of Rejection

Claims 16, 17, 31, 32, 40, 41, and 59-64 are rejected under 35 USC 112, first paragraph, for an alleged non-enablement. The Office Action states that the specification is enabling for inactivation of human O^6-alkylguanine-DNA alkyltransferase ("AGT") *in vitro* but it does not, according to the Office Action, reasonably provide enablement for (a) a method of enhancing chemotherapeutic treatment of tumor cells in a mammal with an antineoplastic alkylating agent that causes cytotoxic lesions at the O^6-position of guanine comprising co-administering a compound or salt of claims 1, 5, or 9 and an antineoplastic alkylating agent which causes cytotoxic lesions at the O^6-position of guanine (claims 16, 17, 59, and 62); (b) a method for treating tumor cells in a mammal by administering a compound or salt of claim 1 (claims 31, 32, 60, and 63); and (c) a method of inhibiting the reaction of O^6-alkylguanine-DNA alkyltransferase with an alkylated DNA by reacting *in vitro* the O^6-alkylguanine-DNA alkyltransferase with a compound or salt of claim 1 (claims 40, 41, 61, and 64).

In response, applicants submit a Rule 132 Declaration from Melinda Hollingshead, DVM, Ph.D., who is an NIH expert in evaluating the efficacy of anticancer agents. The Declaration, through *in vivo* data, shows that a compound of the claimed invention, O^4-benzylfolate, exhibits antitumor activity, as set forth in paragraph 7 of the Declaration. For example, in the case of SW-620 colon tumor xenografts, single agent therapy with continuous infusion O4BFA resulted in an optimal % T/C of 66%. In addition, there was a demonstrable shift in the slope of the tumor growth curve (see Figure 3, line 1 connecting circles for NSC 730793, 40.0 mg/ml SC, 7 day infusion, Day 8) vs. control line 2 (QD x 5, Day 8, 2% EtOH in saline)). There is a strong indication that higher doses of O4BFA are likely to produce greater antitumor activity.

Further, as set forth at paragraph 8 of the Declaration, O^4-benzylfolate, in combination with an antineoplastic alkylating agent (BCNU), enhances the efficacy of tumor

reduction in mice. The study conducted against IGR-OV-1 tumors using bolus dosing with O4BF in combination with BCNU offers evidence of activity in that the combination of 6.7 mg/kg BCNU and 200 mg/kg O4BF group produced a tumor growth delay of 55% (Table 3). This can also be seen graphically in Figure 5 by comparing the control line 2 (QD x 4 days, Day 8, 2% EtOH in saline) to the combination treatment line 1(NSC 742482, 200.0 mg/kg /dose IP, Q10H x 2h, Day 8; NSC 409962, 6.7 mg/kg/dose IP, QD x 4 days, Day 9). This tumor growth delay is greater than the growth delay observed when 6.7 mg/kg BCNU alone was administered (28%, Table 3, column 7).

Applicants submit that the foregoing is evidence that the invention of claims 16, 17, 31, 32, 59, 60, 62, and 63 is enabled as required under the statute. Accordingly, the non-enablement rejection of these claims should be withdrawn.

In regards to claims 40, 41, 61, and 64, which are directed to *in vitro* methods of inhibiting the reaction of AGT, applicants submit that the specification provides ample evidence that the compounds of the claimed invention inhibit AGT. See Table 1 at page 18 of the specification which sets forth data for inactivation of human O^6-alkylguanine-DNA alkyltransferase *in vitro* in the absence and presence of calf thymus (ct) DNA. Thus, compounds 1, 2, 4, 5, 6, and 7 show an ED_{50} of 0.045, 0.4, 0.2, 0.09, 0.19, and 0.01 μM, respectively, in the absence of ct DNA and an ED_{50} of 0.45, 0.5, 0.4, 1.83 1.05, and 0.47 μM, respectively in the presence of ct DNA. Table 1 also sets forth data for O^6-benzylguanine, which is a well-known inhibitor of AGT. The ED_{50} values of some of the compounds of the claimed invention are even lower than that of O^6-benzylguanine, which showed ED_{50} values of 0.32 μM (-ct DNA) and 0.12 μM (+ct DNA). Accordingly, the enablement rejection of claims 40, 41, 61, and 64 should be withdrawn.

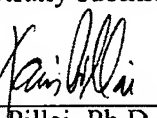
The Office Action states at page 12, lines 6-8: "claim 40 has presently been amended to recite an *in vitro* process. It was previously assumed to be referring to an *in vivo* process, since that is what would be potentially useful." Applicants point out that *in vitro* processes are also useful. For example the *in vitro* process may be used for screening AGT enzymes from various cancer cell types as well mutant forms of AGT.

In view of the foregoing, the non-enablement rejection of claims 40, 41, 61, and 64 also should be withdrawn.

Conclusion

The application is in good and proper form for allowance. A favorable decision is solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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